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Current Good Tissue Practice Requirements (CGTP)

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Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement

Final Rule

Subparts D, E, F of 21 CFR 1271

Final Rule, cont.

- **Published in Federal Register (69 FR 68612) on November 24, 2004**
- **Effective May 25, 2005**
- **Applies to HCT/Ps procured <u>on or after</u> the effective date**

Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement Proposed Rule

- **Published January 8, 2001**
- **Comment period closed on May 8, 2001**
- **47 comments**

CGTPs—CGMPs--QSRs

- **HCT/Ps regulated solely under section “361” of Public Health Service (PHS) Act—CGTPs apply**
- **HCT/Ps regulated as licensed biological products under section “351” of PHS Act and Food, Drug and Cosmetic (FDC) Act—CGTPs and CGMPs apply (21 CFR parts 210 and 211)**
- **HCT/Ps regulated as approved or cleared medical devices under FDC Act—CGTPs and QSRs apply (21 CFR part 820)**

What do CGTPs require that CGMPs don't?

- **All donor eligibility requirements**
- **Exemptions and alternatives (610.9 addresses Equivalent methods)**
- **Quality program (211.22 addresses Quality control unit)**
- **Recovery of HCT/Ps**
- **Tracking (211.196 addresses Distribution records)**
- **In general, if you are in compliance with GMPs, you will be in compliance with GTPs**

What do CGTPs require that QSRs don't?

- **All donor eligibility requirements**
- **Recovery of HCT/Ps (a manufacturer of raw materials or components to be used in the manufacture of a device is not required to register)**
- **In general, if you are in compliance with QSRs, you will be in compliance with CGTPs**

Major Changes from Proposed to Final Rule (when effective)

- **Terminology and Definitions**
  - **“Human cellular and tissue-based products” changed to “*human cells, tissues, and cellular and tissue-based products (HCT/Ps*)”**
  - **The definition of HCT/Ps has been changed from a two-part definition (with two implementation dates) in the Registration and Listing final rule to a one-part definition. 1271.3(d)(1) was deleted, and 1271.3(d)(2) is now <u>1271.3(d)</u>**

Changes, cont.

- **Interim rule published January 27, 2004 is revoked. That rule exempted human dura mater and human heart valves from the definition of HCT/P. As of May 25, 2005, human dura mater and human heart valves are considered "361" HCT/Ps, if they meet the criteria in section 1271.10(a)**

- **Definition of human tissue in 1270.3(j) has been changed so that it now means human tissue for transplantation procured before May 25, 2005**

- **Part 1270 will not be revoked at this time**

Changes, cont.

– ***Adverse reaction:***

- **Proposed "a noxious and unintended response to any HCT/P for which there is a reasonable possibility that the response may have been caused by the product (i.e., the relationship cannot be rules out")**

- **Final "a noxious and unintended response to any HCT/P for which there is a reasonable possibility <u>that the HCT/P caused the response</u>"**

Changes, cont.

– ***Complaint***

- **Proposed "any written, oral, or electronic communication that alleges that an HCT/P has transmitted or may have transmitted a communicable disease.."**

- **Final "…that a <u>distributed</u> HCT/P…"**

Changes, cont.

– ***Distribution***

- **Proposed "any conveyance or shipment (including importation and exportation), whether or not..entirely intrastate, and whether or not possession of the product is taken**

- **Final "any conveyance or shipment (including importation and exportation) of an HCT/P <u>that has been determined to meet all release criteria</u>, whether or not…entirely intrastate. <u>If an entity does not take physical possession of an HCT/P, the entity is not considered a distributor</u>."**

Changes, cont.

– ***HCT/P deviation***

- **Proposed “product deviation”—an event that represents a deviation from CGTP, applicable standards, or established specifications; or an unexpected or unforeseeable event that may relate to the transmission of a communicable disease agent or disease or may lead to product contamination”**
- **Final “a deviation from applicable regulations in this part or from applicable standards, or established specifications that may relate to the prevention of communicable disease transmission or to the prevention of HCT/P contamination”**

Changes, cont.

- ***Processing***
  - **Proposed "any activity performed on an HCT/P other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution. Processing would include, but not be limited to, preparation, sterilization, steps to inactivate and remove adventitious agents, preservation for storage, and removal from storage"**
  - **Final—added "testing for microorganisms"**

Changes, cont.

- ***Processing material*—deleted**
- ***Quality audit***
  - **Proposed "a documented, independent inspection and review of an establishment's activities, including manufacturing and tracking, performed according to procedures, to verify, by examination and evaluation of objective evidence, the degree of compliance with those aspects of the quality program under review**
  - **Final "a documented, independent inspection..<u>related to core CGTP requirements</u>.."**

Changes, cont.

- **Proposed requirements intended to prevent the introduction, transmission, or spread of communicable disease by helping to ensure that the function and integrity of HCT/Ps are not impaired through improper manufacturing**
- **To increase clarity and because of the confusion expressed by comments about the term "function and integrity", this term has been deleted**

Changes, cont.

- **Comments on “function and integrity”**
  - **Define, use a different term (e.g., fit for use) or delete**
  - **?increases risk of disease transmission**
  - **?required to assess for each HCT/P**
  - **?legally supportable under section 361**

Changes, cont.

- **Core CGTP requirements identified, which directly relate to prevention of communicable disease**
- **Other requirements support core CGTP requirements and reference is made to this. Some sections reorganized so that these supporting requirements are listed after core CGTP requirements in each section**
- **Proposed requirements where the connection to the prevention of the introduction, transmission, or spread of communicable diseases may be more attenuated removed**

Changes, cont.

- **Separate section on Recovery of HCT/Ps**
- **Clarifies roles of multiple establishments involved in manufacture (Table)**
- **Not finalizing Subparts D and E with respect to “361” reproductive HCT/Ps**
- **Uses plain language—question and answer format**

Change to 1271.10

- **1271.10 Are my HCT/Ps regulated solely under section 361 of the PHS Act …**
  - **(a)(3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P**

Subpart D--Current Good Tissue Practice

- **Recover, process, store, label, package, and distribute HCT/Ps, and screen/test donors (CGTP includes subpart C), to prevent introduction, transmission, and spread of communicable disease**
- **Ensure that HCT/Ps do not contain communicable disease agents, are not contaminated, and do not become contaminated during manufacturing**
- **Communicable disease agents include viruses, bacteria, fungi, parasites, and TSE agents**

CGTP--General

- **Methods used in, and facilities and controls used for manufacture of HCT/Ps**
- **Narrower in scope than GMPs (GTPs focus on prevention of communicable disease transmission)**
- **Broad goals applicable to the wide range of HCT/Ps**
- **Establishments have the flexibility to determine how to meet goals through their SOPs**

Core CGTPs

- **Requirements most directly related to preventing the introduction, transmission, or spread of communicable disease agents and disease (e.g., facility sanitation; storage at appropriate temp.)**
- **Other requirements support the core CGTP requirements (e.g., procedures for core CGTP requirements; quality program designed to ensure compliance with core CGTP requirements;**

Core GTPs (10)

- **Facilities**
- **Environmental control**
- **Equipment**
- **Supplies and reagents**
- **Recovery**
- **Processing and process controls**
- **Labeling controls**
- **Storage**
- **Receipt, pre-distribution shipment, and distribution**
- **Donor eligibility determination (donor screening and donor testing)**

Compliance with applicable requirements

- **If you perform only certain manufacturing steps, comply with the requirements applicable to the operations you perform**

- **If you engage another establishment, under a contract, agreement or other arrangement to perform manufacturing steps for you, that establishment is responsible for complying with applicable requirements**

Cont.

- **If you have a contract with another establishment to perform some manufacturing steps for you—**
  - **Before entering the contract, ensure that the other establishment complies with applicable CGTPs for the steps it performs**
  - **If you become aware that establishment may no longer be in compliance, take reasonable steps to ensure that the other establishment complies**
  - **If you determine that establishment is not in compliance, terminate the contract**

Available for Distribution

- **The establishment that determines that an HCT/P meets all release criteria and makes the HCT/P available for distribution is responsible for reviewing manufacturing and tracking records to determine that the HCT/P has been manufactured in compliance with subparts C and D**

Compliance with 210, 211, 820

- **Conforming amendments made to these parts to require HCT/Ps that are also regulated as biological drugs or medical devices to follow 1271 subparts C and D**
- **Requirements supplement but do not supersede each other**
- **In the event of a conflict between a requirement in part 1271 and in parts 210, 211, or 820, the regulations more specifically applicable to the product in question supersede the more general**

“Where appropriate”

- **When a requirement is qualified by “where appropriate”, it is considered appropriate unless you can document justification otherwise.**
- **A requirement is appropriate if nonimplementation could reasonably result in the HCT/P not meeting its specified requirements related to prevention of communicable disease transmission, or if you are unable to carry out any necessary corrective action**

Requirements
(* indicates Core CGTPs)

- **Exemptions and Alternatives**
- **Quality Program**
- **Personnel**
- **Procedures**
- **Facilities***
- **Environmental Control and Monitoring***
- **Equipment***
- **Supplies/Reagents***
- **Recovery***

Requirements, cont. (* indicates Core CGTPs)

- **Processing and Process Controls***
- **Process Changes**
- **Process Validation**
- **Labeling Controls***
- **Storage***
- **Receipt, Pre-Distribution Shipment, Distribution***
- **Records**
- **Tracking**
- **Complaint File**

Exemptions and Alternatives

- **Written (or oral under certain circumstances) request to any requirement in subpart C or D. Follow oral request with immediate written request**
- **Submit to Director of Center, together with supporting documentation, including valid scientific data, and information justifying the exemption, or a description of a proposed alternative method of meeting the requirement**

Exemptions and Alternatives, cont.

- **Director may grant exemption or alternative (written, or oral followed by written response) if submitted information justifies an exemption or proposed alternative satisfies the purpose of requirement, and is consistent with goals of protecting public health**
- **Wait until granted by FDA to begin**
- **Keep documentation of FDA's grant, and document start date**
- **Center director may issue an exemption or alternative in a public health emergency**

Quality Program

- **All HCT/P establishments that perform any step in manufacture must establish and maintain a Quality Program that addresses all core CGTP requirements**
- ***Quality program* means an organization's comprehensive system for manufacturing and tracking HCT/Ps in accordance with CGTP requirements; designed to prevent, detect, and correct deficiencies that may lead to circumstances that increase the risk of communicable disease transmission**

Quality Program Functions

- **Establish and maintain procedures relating to core CGTP requirements; review, approve, revise**
- **Ensure that procedures exist for receiving, investigating, evaluating, and documenting information relating to core CGTP requirements (e.g., complaints), and for sharing any information pertaining to the possible contamination of the HCT/P or the potential for transmission of communicable disease by the HCT/P with….**

Quality Program, cont.

- Other establishments that are known to have recovered HCT/Ps from the same donor
- Other establishments that are known to have performed manufacturing steps
- Consignees
- Quarantine and possible recall

Quality Program, cont.

- **Ensure that corrective actions relating to core CGTPs are taken and documented, as necessary—short and long-term action to prevent recurrence**
  - **HCT/P affected, and disposition**
  - **Nature of problem**
  - **Description of corrective action**
  - **Dates of corrective action**

Quality Program, cont.

- **Ensure proper training/education of personnel involved in core CGTP activities**
- **Establish/maintain monitoring systems as necessary (e.g., environmental monitoring)**
- **Investigate/document/trend HCT/P deviations relating to core CGTP requirements; possible reporting to FDA; determine cause and implement corrective and preventive action**

Quality Program, cont.

- **Periodically perform quality audits of activities related to core CGTPs for management review**
- ***Quality audit* means a documented, independent inspection and review of activities related to core CGTPs with the purpose of verifying, by examination and evaluation of objective evidence, the degree of compliance**

Computer Software

- **Validate the performance of computer software for its intended use if you rely on software to comply with core CGTPs and if the software is custom software, or commercially available software that has been customized or programmed for you (e.g., software programmed to perform a user-defined calculation, table)**
- **All other software (e.g., commercially available software)—verify the performance for its intended use if you rely upon it to comply with core CGTP requirements**

Computer Software, cont.

- **Validate any changes to software**
- **Document these activities and have the results approved before implementing the software**